

case report

Carotid and brachiocephalic arteries stenosis with long term use of sorafenib

Fatma Maraiki^{*}, Ali Aljubran

King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, MBC11, Riyadh 11211, Saudi Arabia

^{*} Corresponding author. Tel.: +966 500114663. · FMARAIKI@kfshrc.edu.sa · Accepted for publication 30 June 2013

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The risk associated with arterial thromboembolism (ATE) increases with the presence of anti-vascular endothelial growth factor (VEGF). We are reporting a case of transient ischemic attack (TIA) due to stenosis of the carotid and brachiocephalic arteries following long-term treatment with sorafenib for renal cell carcinoma (RCC). The patient is a non-smoker with no known comorbidities and had no history of cardiovascular disease. The patient underwent a right endarterectomy with angioplasty, aortic arch, and brachiocephalic artery angiogram with a stent placed in the brachiocephalic artery.

This is a case of 45-year-old male non-smoker with no known comorbidities and no history of cardiovascular disease. He presented after three episodes of painless hematuria in March 2001. He was diagnosed with renal cell carcinoma (RCC, stage T1, N0, M0), for which he underwent a left radical nephrectomy. Later pathology revealed a clear cell carcinoma and granuloma; and a computed tomography (CT) scan indicated no metastasis.

At a routine follow-up in March 2007, a CT scan revealed a soft tissue mass in the kidney bed, suggesting local recurrence with liver lesions and retroperitoneal lymph nodes. Accordingly, the patient was started on sorafenib (400 mg orally twice a day). The patient then had multiple CT follow-up scans, all of which showed fluctuating measurement of liver lesions and lymph nodes and unchanged soft tissue in the renal bed. The results were considered an indication of stable disease, so treatment with sorafenib was continued.

In November 2009, the patient was referred to medical oncology for further management. The patient also reported symptoms of fever, sweating, and weight loss, as well as a history of contact with open tuberculosis. Accordingly, the patient had fine-needle aspiration (FNA) of one of the retroperitoneal lymph nodes. The results were negative for malignant cells but with the presence of granulomatous inflammation with negative acid-fast bacilli. The treatment plan was to start anti-tuberculosis treatment and to continue sorafenib because the whole picture suggested both

tuberculosis and RCC relapse. The anti-tuberculosis therapy included isoniazide, ethambutol, moxifloxacin, and pyridoxine, none of which have documented drug interaction with sorafenib. The patient's constitutional symptoms improved, and the anti-tuberculosis treatment was continued for the next 18 weeks.

In May 2011, the patient presented with a history of left-side facial and body weakness for three minutes. A CT scan revealed an incidental bilateral carotid artery stenosis. Further CT scans of the aortic arch revealed tight focal stenosis in the proximal brachiocephalic artery [Figs. 1 and 2]. The internal and external carotid arteries were patent. Also identified was a moderate focal stenosis at the origin of the left common artery, with no other stenosis seen in the rest of the left carotid arteries. A CT scan of the brain was negative.

Ultrasound doppler of the carotids revealed severe stenosis at the thoracic part of the right common carotid and the right brachiocephalic artery. Also found were multiple continuous soft atheromatous plaques throughout the right common carotid, resulting in a 60% distal common carotid stenosis. The internal and external carotid arteries were found to be patent but with lower transmitted systolic velocity and waveform of the distal right internal carotid artery (ICA) high in the neck, almost flat (tardus parvus from the carotid bulb upward), with peak systolic velocities ranging between 25 and 24 cm. The left internal and external carotid arteries had no stenosis, with normal



Figure 1. Left upper extremity angiogram shows stenosis in the proximal brachiocephalic artery.

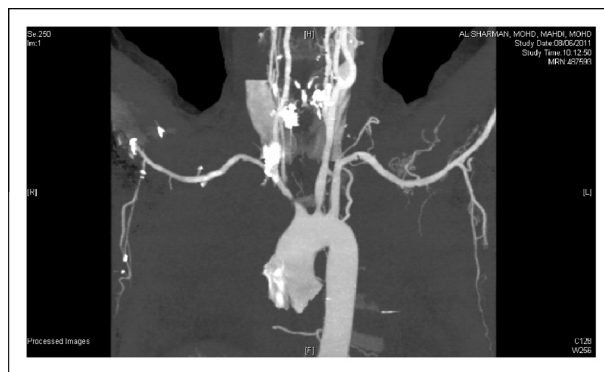


Figure 2. CT aortic arch shows tight focal stenosis in the proximal brachiocephalic artery. Distal to this, the right common carotid, internal carotid and external carotid arteries have diffuse small calibers but are patent. There is also moderate focal stenosis at the origin of the left common carotid artery.

waveform velocities. The left vertebral artery was patent with normal flow.

In July 2011, the patient underwent a right endarterectomy with bovine patch angioplasty, an aortic arch and brachiocephalic artery angiogram, and a stent placement in the brachiocephalic artery, and he was started on clopidogrel with aspirin. His lipid profile (cholesterol 228 mg/dl, HDL 45 mg/dl, LDL 147 mg/dl), and atorvastatin was later prescribed.

At that time, a decision was made to discontinue sorafenib due to the new onset of endarterectomy arterial stenosis that presented with transient ischemic attack (TIA) and the perceived reduced likelihood of RCC recurrence. Two years later, and without sorafenib therapy, there has been no recurrence of RCC. In total, the patient was prescribed sorafenib for 4 years, which is a relatively long duration.

During sorafenib treatment, the patient developed hypertension (blood pressure always above 150/90 mmHg), although this was not treated. Urine dipsticks taken at the time never reported more than

+1 protein. Other laboratory tests performed were always within normal limits, including complete blood counts with differential, renal, and liver function tests. The only side effects identified were grade-one hand-foot syndrome and diarrhea during the sorafenib therapy period.

DISCUSSION

Sorafenib is a tyrosine kinase inhibitor (TKIs) that targets the vascular endothelial growth factor (VEGF). Reported side effects include hypertension, proteinuria, increased risk of bleeding, thromboembolism, hypothyroidism, and gastrointestinal perforation.

We are reporting a case of TIA due to stenosis of the carotid and brachiocephalic arteries following 4 years of sorafenib treatment for RCC.

Our search did not identify any reported carotid artery stenosis with the use of anti-VEGF drugs such as sorafenib, sunitinib, pazopanib, axitinib, vandetanib, and regorafenib, as well as anti-VEGF antibodies such as bevacizumab. Our search did, however, identify two

cases where sorafenib was prescribed and carotid artery stenosis was reported to the FDA through the Adverse Event Reporting System (AERS), as listed on the DrugCite website.¹

The risk of arterial thromboembolism (ATE) associated with anti-VEGF was assessed in two meta-analyses.^{2,3} The first meta-analysis involved bevacizumab, a monoclonal antibody, and the incidence of all grades of ATE were 3.3% (95% CI, 2.0–5.6%), with relative risk (RR) of 2.08 (95% CI, 1.28–3.40; $p = 0.013$) compared to controls.² Interestingly, the analysis also found that bevacizumab significantly increased the risk of high-grade ATE in patients with RCC RR 5.14 (95% CI 1.35–19.64, $p = 0.029$) compared to other solid tumors. However, the risk of cardiac ischemia but not stroke was higher with bevacizumab than in the control group. The second meta-analysis involved sorafenib and sunitinib, TKIs; the incidence of ATE was 1.4% (95% CI 1.2–1.6%) with RR 3.03 (95% CI 1.25–7.37; $p = 0.015$) compared to controls.³ This risk, however, did not differ between the two TKIs (sorafenib versus sunitinib) or tumor types (renal versus non-renal cell carcinoma).

Even though our patient developed ATE with the long-term use of an anti-VEGF, there are reported

cases with much shorter duration of use. There was a report of two cases of cerebrovascular incidents with sorafenib in hepatocellular carcinoma.⁴ In both cases, the patients had no risk factors for cerebrovascular events except gender and age in the second case. Both had normal carotid ultrasounds and normal ECHO. In these cases, both experienced stroke within 5 weeks, which is considered a relatively short time with no development of hypertension.

The risk of ATE seems to be related to atherosclerosis. A study in mice revealed that systemic VEGF inhibition disrupts endothelial homeostasis, accelerates atherogenesis, and can cause a 33% increase in atherosclerotic lesions.⁵

In our case, the carotid stenosis occurred after 4 years, which may be related to the cumulative dose of sorafenib. A recent phase I/II study using sorafenib for solid tumors found the development of grade two and three hand-foot syndrome was associated with cumulative sorafenib exposure ($p = 0.0008$).⁶

CONFLICT OF INTEREST

None declared.

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